



## **Call for uniform neuropsychological assessment after aneurysmal subarachnoid hemorrhage: Swiss recommendations**

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**Abstract:** **BACKGROUND** In a high proportion of patients with favorable outcome after aneurysmal subarachnoid hemorrhage (aSAH), neuropsychological deficits, depression, anxiety, and fatigue are responsible for the inability to return to their regular premorbid life and pursue their professional careers. These problems often remain unrecognized, as no recommendations concerning a standardized comprehensive assessment have yet found entry into clinical routines. **METHODS** To establish a nationwide standard concerning a comprehensive assessment after aSAH, representatives of all neuropsychological and neurosurgical departments of those eight Swiss centers treating acute aSAH have agreed on a common protocol. In addition, a battery of questionnaires and neuropsychological tests was selected, optimally suited to the deficits found most prevalent in aSAH patients that was available in different languages and standardized. **RESULTS** We propose a baseline inpatient neuropsychological screening using the Montreal Cognitive Assessment (MoCA) between days 14 and 28 after aSAH. In an outpatient setting at 3 and 12 months after bleeding, we recommend a neuropsychological examination, testing all relevant domains including attention, speed of information processing, executive functions, verbal and visual learning/memory, language, visuo-perceptual abilities, and premorbid intelligence. In addition, a detailed assessment capturing anxiety, depression, fatigue, symptoms of frontal lobe affection, and quality of life should be performed. **CONCLUSIONS** This standardized neuropsychological assessment will lead to a more comprehensive assessment of the patient, facilitate the detection and subsequent treatment of previously unrecognized but relevant impairments, and help to determine the incidence, characteristics, modifiable risk factors, and the clinical course of these impairments after aSAH. The need for clinically applicable skin substitutes continues to be a matter of fact. Hypothetically, a laboratory grown autologous skin analog with near normal architecture might be a suitable approach to yield both satisfactory functional and cosmetic long-term results. In this study, we explored the use of human endothelial cells derived from freshly isolated adipose stromal vascular fraction (SVF) in a three-dimensional (3D) co-culture model of vascularized bio-engineered skin substitute. **METHODS** The SVF was isolated from human white adipose tissue samples and keratinocytes from human skin biopsies. The SVF, in particular endothelial cells, were characterized using flow cytometry and immunofluorescence analysis. Endothelial and mesenchymal progenitors from the SVF formed blood capillaries after seeding into a 3D collagen type I hydrogel in vitro. Subsequently, human keratinocytes were seeded on the top of those hydrogels to develop a vascularized dermo-epidermal skin substitute. **RESULTS** Flow cytometric analysis of surface markers of the freshly isolated SVF showed the expression of endothelial markers (CD31, CD34, CD146), mesenchymal/stromal cell-associated markers (CD44, CD73, CD90, CD105), stem cell markers (CD49f, CD117, CD133), and additionally hematopoietic markers (CD14, CD15, CD45). Further analysis of white adipose-derived endothelial cells (watECs) revealed the co-expression of CD31, CD34, CD90, CD105, and partially CD146 on these cells. WatECs were separated from adipose-stromal cells (watASCs) using FACS sorting. WatASCs and watECs cultured separately in a 3D hydrogel for 3 weeks did not form any vascular structures. Only if co-cultured, both cell types aligned to develop a ramified vascular network in vitro with continuous endothelial lumen formation. Transplantation of those

3D-hydrogels onto immuno-incompetent rats resulted in a rapid connection of human capillaries with the host vessels and formation of functional, blood-perfused mosaic human-rat vessels within only 3-4 days. CONCLUSIONS Adipose tissue represents an attractive cell source due to the ease of isolation and abundance of endothelial as well as mesenchymal cell lineages. Adipose-derived SVF cells exhibit the ability to form microvascular structures in vitro and support the accelerated blood perfusion in skin substitutes in vivo when transplanted.

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## **Call for Uniform Neuropsychological Assessment After Aneurysmal Subarachnoid Haemorrhage: Swiss Recommendations**

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**Presentation at congresses:** The recommendations have been submitted as an abstract to the annual meeting of the Swiss Society of Neurosurgery, as well as for the Vasospasm congress 2015.

**Abstract:**

**Background:** In a high proportion of patients with favourable outcome after aneurysmal subarachnoid haemorrhage (aSAH), neuropsychological deficits, depression, anxiety and fatigue are responsible for the inability to return to their regular premorbid life and pursue their professional career. These problems often remain unrecognized, as no recommendations concerning a standardized comprehensive assessment have yet found entry into clinical routine.

**Methods:** To establish a nationwide standard concerning a comprehensive assessment after aSAH, representatives of all neuropsychological and neurosurgical departments of those eight Swiss centers treating acute aSAH have agreed on a common protocol. In addition, a battery of questionnaires and neuropsychological tests was selected, optimally suited to the deficits found most prevalent in aSAH patients that was available in different languages and standardized.

**Results:** We propose a baseline inpatient neuropsychological screening using the Montreal Cognitive Assessment (MoCA) between days 14-28 after aSAH. In an outpatient setting at 3 and 12 months after the bleeding, we recommend a neuropsychological examination, testing all relevant domains including attention, speed of information processing, executive functions, verbal and visual learning/memory, language, visuo-perceptual abilities, and premorbid intelligence. In addition, a detailed assessment capturing anxiety, depression, fatigue, symptoms of frontal lobe affection, and quality of life should be performed.

**Conclusion:** This standardized neuropsychological assessment will lead to a more comprehensive assessment of the patient, facilitate the detection and subsequent treatment of previously unrecognized but relevant impairments, and will help to determine the incidence, characteristics, modifiable risk factors and the clinical course of these impairments after aSAH.

**Key words:** aneurysmal subarachnoid haemorrhage; neuropsychological assessment; cognitive deficits; psychosocial outcome; test battery; Swiss standard; standardized assessment

## **INTRODUCTION**

Some decades ago, neurosurgeons, neuroradiologists and neurointensive care physicians struggled to save the pure life of patients who had suffered from aneurysmal arachnoid haemorrhage (aSAH). Meanwhile, outcomes have improved due to less invasive aneurysm occlusion, newly introduced treatment options, and evidence-based managing guidelines.[40] However, up to a third of all aSAH patients still die as a consequence of severe brain damages in the pre-hospital phase or delayed brain injury in the subacute phase. On the other hand, however, a significant proportion of patients with low- or high-grade aSAH respond well to resuscitation and aggressive treatment and keep or regain their functional independence.

In clinical practice, neurovascular surgeons frequently encounter patients, who survive the aSAH and seem to be functionally more or less independent, without any obvious neurological or cognitive deficits. Traditionally, those patients are assessed by means of rather imprecise neurological grading scales such as the Glasgow Outcome Scale (GOS) or the modified Rankin Scale (mRS). Still, many of these patients need weeks or months to regain their premorbid level, and resume work, if at all. Also, a majority of patients with an aSAH have to reduce their workload significantly, undergo professional retraining to a less demanding occupation, or have problems in relationships, family life, or leisure activities, indicating post-haemorrhagic difficulties due to e.g., cognitive deficits, depression, fatigue, or post-traumatic stress disorder.[28, 47, 48, 56, 57, 68] These facts clearly call for a more comprehensive assessment of those patients. Accordingly, many studies on this matter have revealed a strikingly high incidence of neuropsychological deficits (NPD) in the population of aSAH patients.[1, 28] These are, according to a body of literature, determinants of functional independence, return to work, and health-related quality of life (HRQoL) after aSAH.[1, 11, 29, 37, 47, 48, 50, 56, 57] These findings have prompted us to reconsider the way aSAH patients are managed in Switzerland today.

## **OBJECTIVE**

Our aim is to establish a nationwide uniform, standardized and validated neuropsychological assessment battery that is optimally suited to assess the most prevalent deficits in aSAH patients. This new set of tools must be available in different languages (i.e., German, French, Italian, and English). It is the goal of this recommendation to improve the management of aSAH patients in Switzerland by using a pragmatic approach. The specific aspects of these recommendations are a) to offer guidelines concerning a comprehensive neuropsychological assessment for every aSAH patient, b) to improve communication between neurosurgeons, neuropsychologists, rehabilitation units, and general practitioners, c) to expend health-care resources responsibly by implementing a standardized assessment to avoid redundant examinations by multiple institutions.

## **METHODS:**

A workgroup consisting of representatives of the neurosurgical departments and neuropsychological

units of all eight Swiss centers treating acute aSAH (in the following called “the panel”), namely the Kantonsspital Aarau (KSA), Universitätsspital Basel (USB), Inselspital Bern (ISB), Hôpitaux Universitaires de Genève (HUG), Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne), Ente Ospedaliero Cantonale (EOC, Lugano), Kantonsspital St.Gallen (KSSG), and the Universitätsspital Zürich (USZ) that had joined their forces for the Swiss SOS study ([www.swiss-sos.ch](http://www.swiss-sos.ch)), were engaged in several face-to-face meetings and intense interpersonal communication between 09/2012 and 01/2015.

Based on a literature review on neuropsychological testing as well as HRQoL- and return to work outcomes after aSAH, available tests and questionnaires were collected and selected according to their sensitivity, validity and utility in the population of aSAH patients. Only well standardized tests and, from a more practical point of view, tests available in the three major languages of Switzerland (German, French, and Italian) were considered. Dissent was solved by personal discussion between the members.

The panel agreed on a standardized approach (Figure 1) based on clear inclusion and exclusion criteria (Table 1) concerning the neuropsychological assessment of aSAH patients. Along with a comprehensive interview the neuropsychological assessment battery had to fulfil the following criteria:

- Applicability in the clinical routine, i.e., considering both the reasonability to the aSAH patient, as well as the working capacity of the neuropsychologists
- Choice of tests that are sensitive, standardized, and valid including their availability in three official Swiss languages, i.e., German, French, and Italian
- Inclusion of tests / questionnaires that depict the areas of impairment that are most commonly affected in aSAH patients according to the current literature,[1, 28, 29, 47, 48, 56, 57, 70, 81-83] namely a) attention, b) processing speed, c) executive functions, d) verbal and visual memory, e) language, reading, writing and calculation, f) visuo-perceptual abilities, g) premorbid intelligence, h) depression, i) anxiety, j) fatigue, and k) HRQoL
- Encumbers the health insurance system with reasonable expenses and helps to prevent unnecessary expenses by directing the patients into the right path as early as possible

Data of patients included in the Swiss SOS study is reported in this work. Written informed consent was obtained from all of these participants. Both local institutional review boards approved the study (Geneva: Autorisation générale Protocole n° 11-233R (NAC 11-085R); St.Gallen: EKSG 12/016/1B).

## RESULTS

Our interdisciplinary recommendations concerning the implementation of a standardized assessment including neuropsychological, functional, and HRQoL outcome into clinical routine have already been introduced at some of the centers in Switzerland and will soon be established on a nationwide basis. It is meant to serve the individual patient by detecting potential cognitive deficits as well as psychosocial impairment and rendering subsequent support and therapy as early as possible. A second goal of this

initiative is the acquisition of the detailed outcome data for scientific purposes within the framework of the Swiss SOS study.[66] We encourage other physicians to apply the same protocol in order to enable international comparison of standardized, detailed outcome measures and thereby significantly foster clinical research.

### **Recommendation 1: Whom to test?**

In general, all aSAH patients deserve to receive a comprehensive assessment. However, in practice certain factors need to be taken into consideration leading to the exclusion criteria outlined in Table 1. If a detailed neuropsychological testing at one point is not possible due to functional impairments that are a consequence of the incidence itself, however, patients should not be generally excluded from further testing. It is well known that functional impairments often resolve over time, so that those patients should be re-evaluated later.

Thus, if deficits are too severe on the first encounter on day 14 in the subacute phase, cognitive screening should be postponed until day 28 (Figure 1). Irrespective of the degree of impairment in the subacute phase, all aSAH patients should be scheduled for a thorough examination at month 3 and 12 post haemorrhage (see below). At these time points, a screening will help to determine if the comprehensive assessment can be carried-out. Lastly, detailed neuropsychological testing of patients with a formal education of less than 7 years is problematic, as normative data is rarely available, and the results are difficult to interpret. Optionally, the remaining assessment tools (i.e., questionnaires and the Montreal Cognitive Assessment (MoCA)) may be performed in those patients.

### **Recommendation 2: When to test?**

A scheme providing an overview of the time axis of the assessments is presented in Figure 1. In the acute phase of aSAH (0-14 days post-aSAH), a neuropsychological assessment is not reasonable or possible in a high percentage of patients as they may have a reduced state of vigilance and/or attention span. Patients may still be comatose or have to undergo intensive treatment despite being awake, including e.g., strict bed rest and hypertensive treatment for cerebral vasospasm (CVS), resulting in the inability of the patient to undergo testing at this time.

In the subacute phase (14-28 days post aSAH), we propose using the Montreal Cognitive Assessment (MoCA) as a standard,[49] which is a short, simple-to-perform screening tool with a broad applicability and good validity for aSAH.[81-83]. Additional tests can be added to the baseline evaluation at the discretion of the neuropsychologist to evaluate the need for an in- or outpatient (neuropsychological) rehabilitation program. We recommend administering the MoCA at **day 14 post-aSAH**, if possible. If the patient is unable to be tested at day 14 (e.g. comatose, intubated, etc.), the MoCA can be postponed day-by-day until day 28 post-aSAH. If the MoCA cannot be administered until day 28, the patient will not be tested at baseline. Most of these patients present with unfavourable outcome at hospital discharge, so that the physician can usually decide for himself whether a transfer to an



inpatient rehabilitation (potential for recovery) or nursing home (no potential for recovery) is necessary.

**Three months after aSAH**, the MoCA should be repeated as a screening in an outpatient setting (the neuropsychologist should consider using parallel versions!). If the MoCA score is  $\geq 15$  points, a comprehensive, outpatient neuropsychological assessment including a face-to-face interview, a standardized test battery and questionnaires should be performed. Patients not qualifying for the complete neuropsychological examination at three months should however be re-assessed 12 months post-aSAH. If the full neuropsychological assessment is performed and patients are unable to do the whole examination due to fatigue for example, some subtests can be left out (at the discretion of the neuropsychologist) or the assessment can be dispensed to two examination dates. This examination is helpful to evaluate return to work, or the working capacity in those patients that have already restarted their professional life.

**Twelve months after aSAH**, a second comprehensive outpatient neuropsychological assessment (including the MoCA with a cut-off  $\geq 15$  points) should be performed in every patient at follow-up, in order to estimate the course of possible cognitive deficits, and other symptoms such as anxiety, depression, fatigue, behavioural problems or difficulties related to HRQoL. This visit is important to assess the natural course of symptoms or efficacy of the therapy applied, and if further steps are needed.

### **Recommendation 3: How to test?**

The following recommendations only apply to the follow-up examinations at 3 and 12 months post-aSAH, as in the subacute phase only the MoCA is performed (see above). The examination basically consists of three parts: 1) the interview, 2) the subjective questionnaire-based evaluation, and 3) the detailed neuropsychological assessment. It is important to note that part 1) and 2) should be applied to every patient, while not every patient qualifies for part 3). The complete examination comprising all three parts should take approximately 2.5 hours. Depending on the patients' condition, a split of the assessment should be considered.

#### *Part 1): Baseline interview, including working status and important life events*

The assessment should begin with a structured patient interview, where important patient characteristics are captured. These should include: age, gender, handedness (right/left/both), native language and language of examination, developmental- or learning disabilities (No/Yes, Type?), previous CNS comorbidities (e.g. head injuries, epilepsy, stroke, depression, anxiety), current medication, the consumption of cigarettes (number per day), alcohol (drinks per day), or further drugs. To evaluate the premorbid situation, the education in years and highest educational level (e.g., university degree, doctorate, apprenticeship, etc.) must be assessed. To estimate the impact of aSAH on the occupational career, both types of occupation before and after aSAH according to the International Standard Classification of Jobs (ISCO-88 COM),[75] the workload in percent (before and after aSAH), as well as the last day of work before- and the date of work resumption after aSAH

should be recorded.[50] To cope with the social impact of the disease, we suggest inquiring the family situation (e.g. marital status) before and after aSAH. Before any neuropsychological examination, the patient should be asked about self-perceived cognitive symptoms before- and after aSAH and whether a neuropsychological examination had ever been performed before the aSAH. A sample of our structured interview sheet can be downloaded online from Supplementary Table 1.

*Part 2): Questionnaires for anxiety, depression, fatigue, behavioural abnormalities, and HRQoL*

Questionnaires outlined in Table 2, collecting information on anxiety, depression, fatigue, behavioural abnormalities as probable symptoms of frontal lobe affection, and HRQoL are an essential part of the neuropsychological assessment.

*Part 3): Neuropsychological test battery*

The detailed neuropsychological testing is reserved to those patients that fulfil none of the exclusion criteria outlined in Table 1. After re-administering the MoCA at the beginning of the examination, one should refrain from further detailed neuropsychological testing of patients scoring <15 points (reason outlined above). All patients scoring  $\geq 15$  points on the MoCA, however, qualify for a more detailed assessment using the test battery proposed in Table 3. The following domains are considered to be most important in aSAH patients and are thus covered by the test battery: attention, executive functions, processing speed, memory, visuo-perceptual and constructional abilities, as well as language.[1] As mentioned, parts of the test battery may be omitted or divided and performed on two separate occasions, if the patient is unable to perform the complete assessment in one session (e.g. limited span of attention, fatigue, aphasia). For the second examination (at 12 months), parallel test versions should be used – whenever possible – to prevent bias due to practice effects.[64]

To conclude the assessment, observations made during the neuropsychological examination should be documented as proposed in Supplementary Table 2.

## **DISCUSSION**

We have undertaken efforts to develop and establish a nationwide standard that offers guidelines for a comprehensive assessment of aSAH patients that includes neuropsychological, psychosocial and HRQoL-implications of the disease. This proposed standard has been implemented in some of the Swiss neurovascular departments already, and is going to be adopted by the remaining departments in the near future. With this step we hope to accurately diagnose the presence and magnitude of neuropsychological deficits (NPD), anxiety, depression, fatigue, and behavioural problems in the individual patient.

A detailed assessment identifying the characteristics and magnitude of the patient's individual deficits, helps to initialize a specific therapy as early as possible and thereby maximize the chance of recovery. Detection of these impairments is crucial, as they are known to have a high incidence and impact on the subjects' well being, the HRQoL and ability to work after aSAH.[11, 53, 78] Also, the early

identification of deficits may help both the patient and his/her relatives to understand the reason for possible difficulties in the psychosocial, familiar, recreational and occupational re-integration, absorb future complications, and be helpful to estimate the patient's short- and long term working capacity. As such, a recent study demonstrated that the neuropsychological outcome 12 months after aSAH could predict the ability to work even ten years after the assessment.[78] Since aSAH patients are generally much younger than patients experiencing ischemic stroke for example, the significance of this estimation and its impact on our society becomes obvious. A detailed assessment is not possible in every patient, largely depending on his/her individual clinical condition. As such we have introduced the MoCA as a screening tool (with the cut-off  $\geq 15$  points) to decide whether or not the comprehensive test battery can be applied at 3 and 12 months post-aSAH. This approach both avoids bothering severely impaired patients and saves health care resources. There are no previous studies defining a similar cut-off, but it has been our experience in a pilot project on n=61 patients that a extensive assessment is not possible in patients scoring  $< 15$  points on the MoCA. In the subacute phase (14-28 days post-aSAH) 48.2% of patients scored  $< 15$  points in the MoCA, with the rate dropping to 25.8% and about 10% at 3- and 12 months post-aSAH. These numbers are in accordance with previous literature [81-83] and indicate that the battery can be applied to most of the surviving patients. Those that do not qualify for a more detailed assessment should be considered cognitively impaired and benefit from adequate support (ergotherapy, specialized cognitive training). However, further detailed testing of these patients using a 2.5-3h face-to-face interview is impossible and little meaningful at this time.

Standardizing the way aSAH patients are managed and assessed in a nation wide manner is a unique chance to study the incidence, evolution, and risk factors for psychosocial impairments. As such, we intend to record the results of the assessment in all patients that agree to participate in the prospective multicentre Swiss SOS study ([www.swiss-sos.ch](http://www.swiss-sos.ch)).[66] By using the structures of this already well-established network, we can correlate psychosocial impairments to specific aspects of the disease and its treatment and profit from this massive gain of information not only from a scientific perspective, but also by means of an improved assistance of the individual patient. Identifying risk factors (especially modifiable risk factors) for neuropsychological outcome after aSAH is essential to facilitate their future prevention. As these are only beginning to be determined,[70] there is a great need for further progress in clinical research. Only recently it was reported that characteristics of NPD after aSAH differ from those of other types of intracranial haemorrhage, as being more pronounced, but also more reversible.[10] This is good news, as impairment seems to be modifiable, again stressing the importance of its detection and subsequent therapy.[70]

Until today, however, neuropsychological outcome after aSAH is not always assessed, and especially underreported in scientific publications on aSAH. A recent meta-analysis demonstrated the paradox between a high incidence of NPD on the one hand, and an extremely low frequency of their standardized assessment and scientific research in this area on the other hand.[71] In addition, the current assessment of NPD shows a great variability in published clinical series, and is often subject to profound selection bias. The need to obtain a general overview of neuropsychological outcome of aSAH patients remains largely unmet. Reasons are the missing neuropsychological infrastructure in

some countries, and the challenge of such an endeavour with neurosurgeons and neuropsychologists of multiple centers having to cooperate tightly.

The medical care in Switzerland is generally highly developed and complex diseases such as aSAH are treated using the best standards of care. All aSAH patients surviving the initial haemorrhage and being admitted to a hospital in Switzerland as well as Liechtenstein and some neighbouring regions of Italy, France, Austria and Germany, are transferred to one of the above-mentioned centers for subsequent treatment. Owing to geographical and epidemiological features, and the complexity of the disease and its treatment, it has been decided in the context of the “Hochspezialisierte Medizin” (HSM; highly-specialized medicine) discussion that aSAH should only be treated at the eight tertiary neurovascular centers listed above that cooperate tightly within the framework of the Swiss SOS study.[66] Especially for a complex and relatively infrequent disease such as aSAH, standardized care, a focused medical supply and both quality assessment and control as well as scientific collaborations on a national level are warranted. In Switzerland, the local circumstances render the implementation of the proposed standard possible.

## **Limitations**

The choice of tests and questionnaires that are depicted in Tables 3 and 4 constitute a compromise of experiences with aSAH patients, the availability of the tests in multiple languages, existence of normative data, alternate forms, as well as their reproducibility, cost-effectiveness, and meaningfulness for patient and scientific evaluation. Of note, besides the core test battery presented here, additional tests may be added to evaluate more specific deficits related to specific localisation of the aSAH or its consequences (e.g., ruptured aneurysm of the anterior communicating artery with a frontal intracerebral haematoma – tests for social cognition; cerebral vasospasm of the right middle cerebral artery – mental rotation test). Still, the effect of fatigue in a significant percentage of patients should not be underestimated and the assessment kept as short as possible. From a scientific point of view, a further complete testing 60 months after aSAH would be of great interest to gain more insights into the clinical course of the psychosocial evolution of our patients. However, as this will be of little value to the clinical decision-making of the individual patient, the long-term testing cannot be included into this standard, which was primarily developed from a clinical point of view to improve the patient care.

The fact that a pragmatic approach was chosen over a systematic evidence-based method (Delphi method) might be considered as limitation. The agreement on this test battery was arrived at an internal discussion of the advantages and drawbacks of available tests, under the special consideration of previous literature. Personal experience of the panel members with this patient population supported the decision-making, which is why our proposed standard is not strictly scientific or evidence-based. Still, almost every test included in the battery proposed here has been demonstrated to be sensitive, valid and utile in prior works on aSAH.[4, 6, 8-11, 13, 14, 16, 17, 19-31, 33-37, 42-45, 47, 48, 50-53, 55, 56, 59, 62, 64, 65, 67, 70-74, 77-79, 81-83] Establishing a standard is a big challenge for a single department and even more so for a whole nation with multiple language areas. By using a pragmatic approach though we have been able to define a reasonable standard that

might be adopted by further departments or countries in order enable international comparison of the results. Future works of this group will aim at reporting results using this battery that will help to estimate the burden of aSAH in an unselected nation-wide patient population. On-going review of these results will help to optimize and possibly shorten this current standard in the future to enhance broad applicability, especially important for areas with fewer resources.

## **CONCLUSION**

We have developed a nationwide standard for a comprehensive assessment of patients after aneurysmal subarachnoid haemorrhage that includes neuropsychological, psychosocial and HRQoL-aspects of the disease. This standard will be implemented in all Swiss neurovascular departments treating acute aSAH and aims to accurately diagnose the presence and magnitude of neuropsychological deficits, as well as anxiety, depression, fatigue, and HRQoL in the individual patient in order to render subsequent treatment as early as possible. Scientific analysis of these detailed outcomes will help to understand the burden of this disease on patients and society, and enable fascinating insights into the pathophysiology of aSAH.

## TABLES

**Table 1:** Recommended criteria whether or not to perform a detailed neuropsychological testing as part of a standardized outcome assessment.

### Inclusion criteria:

- Patient's age  $\geq 18$  years

### Exclusion criteria:

- Education  $< 7$  years
- Impaired vision (defined as not being able to read the tests / instructions even by aid of magnifying glasses)
- Impaired hearing (defined as not being able to follow a conversation despite hearing aids)
- Insufficient language skills before aSAH (aphasic deficit as consequence of aSAH is not an exclusion criterion)
- Unable to complete the assessment in German, French, or Italian
- Impaired vigilance (defined as patients not responding to any oral or visual communication)

**Table 2:** Selection of questionnaires proposed at 3 and 12 months post-aSAH to collect information on anxiety, depression, fatigue, symptoms of frontal lobe affection, and health-related Quality of Life.

- Hospital Anxiety and Depression Scale (HADS) [9, 56, 57, 76]
- Multidimensional Assessment of Fatigue (MAF) [37]
- Frontal Systems Behavior Scale (FrSBe) [41]
- Short-form 12 (SF-12, including the Mental Component Scale (MCS) and Physical Component Scale (PCS), the subscales of Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health) [34, 74]
- Euro-QoL (EQ5D) [62]

**Table 3:** Recommended test-battery for a comprehensive neuropsychological assessment 3 and 12 months after aneurysmal subarachnoid hemorrhage. AVLGT = Auditiv-verbaler Lern- und Gedächtnistest (as adaptation of the Rey Auditory Verbal Learning Tests (RAVLT)); MoCA = Montreal Cognitive Assessment; RO-CFT = Rey-Osterrieth Complex Figure Test; SLP = Standardized Link's Probe; TAP = Computerized Test of Attentional Performance; TMT = Trail Making Test.

Domain	Test / subtest
<i>Cognitive screening</i>	- MoCA [81-83]

<i>Attention</i>	<ul style="list-style-type: none"> <li>- TAP 2.3, using the subtests alertness; divided attention; Go/NoGo (1 out of 2); neglect (92 trials with switching letters) [35, 84]</li> <li>- Verbal [12, 80] and visual [32] span - forward</li> </ul>
<i>Executive Functions</i>	<ul style="list-style-type: none"> <li>- Color-Word Interference Test (Victoria version) [7, 14, 20, 59, 60]</li> <li>- Verbal fluencies (semantic and phonemic) [3, 15, 20, 38, 59]</li> <li>- Design fluency (Five-points test) [12, 20, 61]</li> <li>- Cognitive flexibility (TMT B) [35, 59, 69]</li> <li>- Problem-solving (SLP) [46]</li> </ul>
<i>Cognitive Speed</i>	<ul style="list-style-type: none"> <li>- TMT A [35, 59, 69]</li> </ul>
<i>Memory</i>	<ul style="list-style-type: none"> <li>- Verbal learning and memory (AVLGT) [18, 55, 58]</li> <li>- Nonverbal Memory (RO-CFT– delayed recall) [1, 2, 20, 54]</li> <li>- Verbal [12, 80] and visual working memory [32]</li> </ul>
<i>Visual-perceptual abilities</i>	<ul style="list-style-type: none"> <li>- RO-CFT – copy [1, 2, 20, 54]</li> </ul>
<i>Language</i>	<ul style="list-style-type: none"> <li>- Token test [1, 5, 36, 39]</li> <li>- Reading, writing, number processing and calculation (cursory examination)</li> </ul>
<i>Premorbid Intelligence</i>	<ul style="list-style-type: none"> <li>- Similarities [7, 12, 80]</li> </ul>
<i>Eye–hand coordination and motor speed</i>	<ul style="list-style-type: none"> <li>- Grooved Pegboard Test [12, 14, 20, 63]</li> </ul>

## FIGURE LEGENDS

**Figure 1:** Scheme of the Swiss standardized assessment after aSAH. MoCA = Montreal Cognitive Assessment. \* = Testing should be performed on day 14 after aSAH, if possible. If not possible (e.g. patient still on respirator, comatose, not safe to perform the testing for medical reasons), the MoCA can be performed any day until day 28 after aSAH. If needed for the decision whether or not the patient needs an inpatient rehabilitation program, the neuropsychologist can add specific tests at his discretion.

**CONFLICTS OF INTEREST:**

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript

**INFORMED PATIENT CONSENT:**

Data of patients included in the Swiss SOS study is reported in this work. Written informed consent was obtained from all of these participants. Both local institutional review boards approved the study (Geneva: Autorisation générale Protocole n° 11-233R (NAC 11-085R); St.Gallen: EKSG 12/016/1B).

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